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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	04995.0032-0	7721

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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/215,163	Stinson et al.
Examiner	**Art Unit**
Jennifer Graser	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jan 14, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Jan 14, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☐ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

4. ☒ Applicant's reply has overcome the following rejection(s):
   The rejection of claims 23 and 29 under 35 U.S.C. 112, second paragraph.

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see former Office Action mailed 5/23/01.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: *none*

   Claim(s) objected to: *none*

   Claim(s) rejected: *1, 2, 13-20, 23, and 29*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

11. ☐ Other:

J Graser 2/26/02

JENNIFER GRASER
PRIMARY EXAMINER
ART UNIT 1645

ADVISORY ACTION

1. See former Office Action.

Supplemental Brief Response to Newly presented arguments submitted After Final.

2. Claims 1, 13-20, 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized monoclonal antibody which binds to Shiga toxin I, does not reasonably provide enablement for 'humanized monoclonal antibodies which bind to Shiga toxin type 1 variants'(claim 13 and 16) or 'fragments or derivatives' from a humanized monoclonal antibody which binds to Shiga toxin type 1, nor does the specification enabled for humanized monoclonal antibodies wherein 'at least part of' the variable region is from SEQ ID NO:42 and SEQ ID NO:43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification discloses humanized monoclonal antibodies which will bind to Shiga type I toxin and humanized monoclonal antibodies which contain "at least part of the variable region from SEQ ID NO:42 and 43. The specification states that substitutions, additions, or deletions may be made to the sequence encoding the antibody; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the antibody to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid

substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The changes allowed for in the claims could cause a detrimental effect to the antibody to be produced and could cause total negation of any epitopes which could correctly bind Shiga Toxin I. It is unclear that an immunogenic epitope binding region would be retained in the fragments and derivatives. Additionally, the specification has not adequately set forth the location of immunoprotective epitopes. The specification sets forth nothing less than a humanized monoclonal antibody which can bind Shiga Toxin I as exemplified the deposits recited in claim 2. Selective point mutation to one key antigen residue could, in practical terms, eliminate the ability of the antibody to recognize the Shiga I toxin. If the range of decreased binding ability after single point mutation of an antibody varies, one could expect point mutations in the antibody to cause varying degrees of loss of binding, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes could result in a complete loss of binding. An antibody having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antibody that is precipitously or progressively unrecognizable and unable to bind to the Shiga toxin. Thus, antibodies of different levels of homology may not recognize by the native Shiga Toxin I. Given the lack of guidance contained in the specification and the

unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation..

Additionally, claim 2 recites humanized monoclonal antibodies having the same binding specificity as three deposited monoclonal antibodies. Applicants argued in the former Office Action that a deposit of these ATCC antibodies was not required because they were publicly known and available as evidenced by the prior art relied upon in the 35 USC 103 rejection. This was persuasive with respect to the deposited antibodies. However, claim 2 is drawn to antibodies with the same binding specificity as the deposited antibodies. According to prior art references, monoclonal antibodies can be readily produced; however, the total characterization of a monoclonal antibody is a long and complex procedure which varies widely with the intended use of the antibody. A general point is that if a single hybridoma has been produced and is intended for a specific function it is *unlikely* that the antibody produced will have all the required characteristics (Campbell, Laboratory Techniques, Vol. 13, 1984). Campbell teaches that it is a waste of both reagents and time to attempt full characterization of an antibody which is not obtained from a fully cloned cell line. See Chapter 10, specifically page 186. While the specification provides enough information for one of ordinary skill in the art to produce hybridoma cell lines secreting antibodies with similar properties as monoclonal antibodies 13C4, and 11E10, reproduction of an identical cell line and antibody is an extremely unpredictable event (see Campbell above). Accordingly, it would take one of skill in the art undue

experimentation to produce humanized antibodies with the identical binding specificity as the deposited antibodies of claim 2.

Response to Arguments:

The deposited antibodies listed in claim 2 should be claimed. Monoclonal antibodies "with the same binding specificity" are not allowable. It is unclear what this binding specificity is. A general point is that if a single hybridoma has been produced and is intended for a specific function it is *unlikely* that the antibody produced will have all the required characteristics (Campbell, Laboratory Techniques, Vol. 13, 1984). Campbell teaches that it is a waste of both reagents and time to attempt full characterization of an antibody which is not obtained from a fully cloned cell line.

Applicants arguments have been considered but are not deemed persuasive. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The monoclonal antibody itself is required.

Claim Rejections - 35 USC § 103

3. Claims 1, 2, 13-20, 23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Speirs et al (Can. J. Microbiol., 1991, 37: 650-653) or O'Brien et al (US 5,747,272) in view of Shitara et al (US 5,866,692).

Speirs et al teach the 11E10 monoclonal antibody which binds to shiga-toxin II. See especially abstract, page 651, first column).

O'Brien et al also teach the 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain. See especially column 4, lines 38-58.

Shitara et al teach a method of producing humanized chimera antibodies. Humanized chimera does not cause formation of anti-mouse immunoglobulin antibody in the body of the patient and therefore side effects are reduced. See abstract and column 1, lines 10-48).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to synthesize and express the humanized chimera antibody which binds to the shiga-like toxin type II. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs and O'Brien because doing so would avoid the side effects caused by anti-mouse immunoglobulin antibody when monoclonal antibody is administered, yet it would still maintain an effective therapeutic effect. The humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Response to Applicants' arguments:

In response to applicant's arguments against the references individually, i.e., Shitara, one cannot show nonobviousness by attacking references individually where the rejections are based

on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Shitara is merely cited to show that the process of humanizing monoclonal antibodies was well known in the prior art. The instant claims do not recite a specific DNA sequence.

Further, Applicants have argued that just because a technique is common does not necessarily create a motivation to combine it with another technique or reagent. They argue that even if humanizing monoclonal antibodies is a common technique, this does not suggest that all monoclonal antibodies, whether directed to human pathogens or not, should be humanized. This has been fully considered but is not deemed persuasive. It is maintained that the humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Applicants cite the abstract of Iwahashi et al which describes the humanization of a murine monoclonal antibody. They argue that this abstract is an example that humanization of antibodies does not necessarily circumvent the problem of immunogenicity that humanizing tries to overcome. This has been fully and carefully considered, but is not deemed persuasive. Iwahashi et al demonstrate that those of ordinary skill in the art routinely humanize monoclonal antibodies to determine their clinical potential. This reference supports the rejection of record. Obviousness does not require absolute predictability of success. Indeed, for many inventions that

seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. However, Iwahashi et al does provide absolute success with regard to the humanization of a monoclonal antibody. The current invention is drawn to a product, not a method. The prior art teaches that it would have been obvious to make this product. Applicants' arguments with respect to Merluzzi et al have been considered but are not deemed persuasive.

4. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

J Graser 2/26/02

Jennifer Graser
Primary Examiner
Art Unit 1645